REMARKS

A check for the fee for a three month extension of time accompanies this response. Any other fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-67 and 79-89 are pending in this application. Claims 1-11, 15-18, 28-38, 51-55 and 79-81 are examined on the merits. Claims that do not read on the elected species are retained for possible rejoinder upon allowance of a generic claim. Claims 1, 28 and 51, for example, are generic. Claims 1 and 28 are amended to render it clear that the mutants are individually generated and screened. Claim 18 is amended to correct an obvious error; the is-Hit amino acids are in the target protein, not the modified proteins, which are designated LEADS. Claim 80 is amended for clarity. No new matter is added, nor do the amendments change the scope of the claims.

Amendments to the specification include addition of an incorporation by reference of a sequence listing section in accord with 37 C.F.R. § 1.77(b)(5), and amendment of the "Description of the Figures" to bring the specification into compliance with the Sequence Rules set forth in 37 C.F.R. §§ 1.821-1.825. Additional amendments replace attorney docket numbers with the application numbers that were unavailable at the time of filing and correction of the Title of copending application U.S. application Serial No. 10/658,834. The abstract is amended to include additional description as required by the Examiner.

The Sequence Listing is amended to include sequence of the polypeptide set forth in Figure 12 in accord with the Sequence Rules set forth in 37 C.F.R. §§ 1.821-1.825. Basis for the amendment can be found in Figure 12. The amendment at page 9 of the specification incorporates a SEQ ID NO identifier for the aforementioned protein sequence in the Description of the Figures for Figure 12.

An executed Declaration of Manuel Vega pursuant to C.F.R. §1.132 accompanies this response.

THE ELECTION/RESTRICTION REQUIREMENT

It respectfully is submitted that claims, such as claims 1, 15 and 28 are linking claims. As such, upon allowability of any linking claims, any groups linked thereby must be withdrawn. Accordingly, non-elected claims are retained for possible rejoinder upon allowance of a linking (genus) claim.

INFORMATION DISCLOSURE STATEMENT

A supplement Information Disclosure Statement is filed under separate cover. It addresses the issues raised in the instant Office Action.

OBJECTIONS TO THE SPECIFICATION

Abstract

While there is no requirement that an abstract include at least 50 words as suggested by the Examiner, it is amended herein to include additional description.

Description

The Examiner's attention is directed to the Preliminary Amendment, mailed March 04, 2005, which corrected the typographical error on page 1, line 18, and the typographical error on page 5, line 28, that were noted by the Examiner.

The specification is amended at page 1, line 15, and at page 40, line 28, to correct the typographical errors noted by the Examiner.

Drawings

The substitute Sequence Listing and amendments to the specification provided herewith address the issues raised with respect to the drawings.

THE REJECTION OF CLAIMS 1-11, 15-18 AND 28-38 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-11, 15-18 and 28-38 are rejected under 35 U.S.C. §112, second paragraph, as indefinite on several grounds discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Claims 1 and 28 are rejected in the recitation of "each LEAD protein in a set contains the same amino acid replacement" because it allegedly is unclear whether all LEADS have the same amino acid type replacement or the same replacement at the same locus. In the interest of advancing prosecution, these claims are amended to recite that the locus and amino acid replaced that is replaced is the same in each LEAD protein in a set. This renders it clear that the mutant polypeptides are modified one-by-one at one position at a time, and are screened one-by-one.

Claim 80 is rejected as indefinite in the recitation of "pseudo wild type amino acid." It respectfully is submitted that the claims are read in light of the specification, which defines pseudo wild type amino acid at page 17. In the interest of advancing prosecution, however, this claim is amended to include the definition, thereby rendering the meaning clear.

THE REJECTION OF CLAIMS 1, 4-11, 28-35, 51 AND 52 UNDER 35 U.S.C. §102(b)

Claims 1, 4-11, 28-35, 51 and 52 are rejected under 35 U.S.C. §102(b) as anticipated by Ladner *et al.* (U.S. Patent No. 5,096,815) because Ladner *et al.* discloses a method for generating modified polypeptides in which target amino acids are identified by computer and a collection of mutants is produced and screened. The Examiner states that candidate substitutions are made by a process of site-specific mutagenesis at 5 specific restricted residues, followed by expression of the genes in plasmids in host bacteria and screening for DNA binding. This rejection respectfully is traversed.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). A reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The rejected claims

Independent claim 1 is directed to a method for generating a protein or peptide molecule, having a predetermined property or activity that includes the steps of:

(a) identifying, within a target protein or peptide, one or more target amino acids amenable to providing the evolved predetermined property or activity upon amino acid replacement, wherein each target amino acid is designated an *in silico*-HIT (is-HIT);

(b) identifying one or more replacement amino acids, specific for each is-HIT, amenable to providing the evolved predetermined property or activity to the target protein upon amino acid replacement, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;

(c) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein:

each encoded candidate LEAD protein contains a single amino acid replacement;

each replacement is at the same is-HIT locus, whereby each candidate LEAD protein is the same;

each nucleic acid molecule in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide, whereby the members of each set differ by one amino acid from the members of each of the other sets;

each set is separate from each and all other sets;

(d) individually introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins to produce sets of LEAD proteins, wherein:

the host cells are in an addressable array such that each lead protein is expressed at a different locus in the array; and

each LEAD protein in a set contains the same amino acid replacement;

(e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

Dependent claims specify particulars regarding the method.

Independent claim 28 is directed to a method for generating proteins with a desired property or activity, comprising:

(a) identifying a target protein;

(b) identifying is-HIT target residues associated with the property;

(c) preparing variant nucleic acid molecules encoding variant proteins, wherein each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid at one locus from the target protein at one is-HIT target residue;

(d) separately introducing the nucleic acid molecules encoding each candidate LEAD protein into hosts for expression thereof, and expressing the nucleic acid molecules encoding each variant protein to produce sets of LEAD proteins, wherein:

each candidate LEAD protein in a set contains the same amino acid replacement;

each candidate LEAD protein contains a single amino acid replacement; and

each replacement is at the same locus;

(e) individually screening each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

Thus, in the instantly claimed methods a region for modification of a protein is identified, one amino acid at time in the region is varied and each variant is separately produced and separately screened to identify LEADs. Each variant differs from the unmodified protein at only one amino acid. In dependent claims, variations from different LEADs are combined.

Differences between the disclosure of Ladner *et al.* and the instantly claimed methods

Ladner *et al.* discloses the generation of a "variegated" population of DNA molecules that encode modified polypeptides. This population constitutes a mixture of different DNA molecules that then are used to transform a cell culture. The variegated DNA is a population of molecules that vary at a number of defined loci, typically at two to five bases, where the residues are varied through all 20 amino acids thus producing DNA molecules encoding a number of distinct potential target-binding proteins. The collection of molecules is expressed and screened. Hence the method of Ladner *et al.* differs from the instantly claimed methods in several respects. Ladner *et al.* does not prepare and screen individual mutants separately.

In particular, Ladner *et al.* discloses DNA binding proteins a process designated variegation of genes encoding known DNA binding proteins. The term variegated is defined in Ladner (see col. 12, lines 50-53):

> This application uses the term "variegated DNA" to refer to a population of molecules that have the same base sequence through most of their length, but that vary at a number of defined loci.

Hence the modified polypeptides are varied at number of loci; there is no suggestion for varying the polypeptides at one locus at a time.

Ladner continues at col. 17, lines 19-43:

> The fundamental principle of the invention is one of forced evolution. The efficiency of the forced evolution is greatly enhanced by careful choice of which residues are to be varied. The 3D structure of the potential DNA-binding domain and the 3D structure of the target DNA sequence are key determinants in this choice. First a set of residues that can either simultaneously contact the target DNA sequence or that can affect the orientation or flexibility of residues that can touch the target is identified. Then all or some of the codons encoding these residues are varied simultaneously to produce a variegated population of DNA. The variegated population of DNA is introduced into cells so that a variegated population of cells producing various potential-DBPs is obtained.
>
> The highly variegated population of cells containing genes encoding potential-DBPs is selected for cells containing genes that express proteins that bind to the target DNA sequence ("successful DNA-binding proteins"). After one or more rounds of such selection, one or more of the chosen genes are examined and sequenced. If desired, new loci of variation are chosen. The selected daughter genes of one generation then become the parental sequences for the next generation of variegated DNA (vgDNA).

In Ladner's method, which is for producing DNA binding proteins, residues to be varied are selected and then "all or some" of the residues are varied to produce a "variegated population of DNA" molecules. The application and claims state that the cell culture is transformed

with a variegated gene encoding potential DNA-binding proteins or polypeptides, "where said cells collectively can express a plurality of different but sequence-related potential DNA-binding proteins or polypeptides. " Thus, in the Ladner *et al.* method, regions are identified, and one or more residues are modified in the DNA and populations (i.e. mixtures) of the varied (variegated DNA) are produced, then expressed and the populations are screened.

In contrast, in the instantly claimed method, a region of the polypeptide to be varied is identified, and only one residue at a time is varied, and each modified polypeptide is individually expressed and tested to identify a LEAD(s). Hence Ladner *et al.* fails to disclose several elements of the instantly claimed methods. In particular, Ladner *et al.* fails to disclose a method (claim 1 and dependents) that includes any or all of the steps of:

(1) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein:

each candidate LEAD protein contains a single amino acid replacement, and each replacement is at the same is-HIT locus, wherein each candidate LEAD protein is the same;

each nucleic acid in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide, whereby the members of each set differ by one amino acid from the members of each of the other sets;

each set is separate from all other sets;

(2) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein:

each encoded candidate LEAD protein contains a single amino acid replacement;

each replacement is at the same is-HIT locus, whereby each candidate LEAD protein is the same;

each nucleic acid molecule in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide, whereby the members of each set differ by one amino acid from the members of each of the other sets;

each set is separate from each and all other sets;

(3) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

Further Ladner *et al.* fails to disclose a method that includes any or all of the steps of (claim 28 and dependents):

(1) preparing variant nucleic acid molecules encoding variant proteins, wherein each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid at one locus from the target protein at one is-HIT target residue;

(2) separately introducing the nucleic acid molecules encoding each candidate LEAD protein into hosts for expression thereof, and expressing the nucleic acid molecules encoding each variant protein to produce sets of LEAD proteins, wherein:

each candidate LEAD protein in a set contains the same amino acid replacement;

each candidate LEAD protein contains a single amino acid replacement; and

each replacement is at the same locus;

(3) individually screening each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

Analysis and conclusion

As noted above, Ladner *et al.* fails to disclose elements of any of independent claims 1 or 28 or of claims dependent thereon. Each of these claims requires that each of the polypeptides that is generated differs from the original polypeptide by only one residue, and requires that each polypeptide is expressed separately and screened separately.

The method of Ladner *et al.* involves screening populations of mixtures of proteins encoded by variegated DNA. The encoded proteins contain one or more modifications; the variegated DNA is produced as a mixture of molecules that encode proteins that differ by one or more amino acids, and the proteins are produced and screened as a mixture. There is no disclosure in Ladner for producing individual nucleic acid molecules that encode proteins that differ from the original protein by only one amino acid, nor is there any disclosure for separately expressing screening the encoded proteins as required by all of the pending claims. In the method of Ladner *et al.* the modified proteins contain one or more modifications, the modified nucleic acids are prepared as a mixture and the encoded proteins screened from the mixture. The method of Ladner *et al.* does not include the steps of producing sets of polynucleotides that encode polypeptides that have one amino acid replaced compared to the wildtype (target) protein. Ladner *et al.* does not disclose individually introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins to produce sets of LEAD proteins, where the host cells are present in an addressable arrays, and where each LEAD protein in a set contains the same amino acid replacement. In the method of Ladner *et al.*. mixtures of nucleic acids that encode proteins modified at one or more loci are screened to identify proteins that bind to a target. In contrast, in the instantly claimed methods the polypeptides are produced such that they only differ at one locus from wild type. Each polypeptide is expressed and screened separately.

Furthermore, with respect to claims 1-3, the Examiner states in the Office Action, with respect to the rejection under 35 U.S.C. §103(a), discussed below, that Ladner fails to

"teach use of solid support with wells to analyze each specie of protein." Hence, the Examiner admits that Ladner *et al.* is deficient in teaching all elements of any of claims 1-3.

Therefore for the above reasons, Ladner *et al.* fails to disclose elements of the methods of claim 1 and 28. Thus, it does not anticipate any of claims 1 and 28 nor any claims dependent thereon.

THE REJECTIONS OF CLAIMS 1-3, 6, 15-18, 28, 36-38, 52-55, 79 AND 81 UNDER 35 U.S.C. §103(a)

Claims 1, 6, 15-18, 28, 36-38, 52-55 and 81

Claims 1, 6, 15-18, 28, 36-38, 52-55 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* (U.S. Patent No. 5,096,815) in view of Alam *et al.* (Journal of Biotechnology, volume 65, 1998, pages 183-190) because Ladner *et al.* teaches:

> a method for generating a protein or peptide molecule is discussed. Target amino acids are identified by computer, and candidate substitutions are identified. A collection of mutants with desired properties are produces. They are expressed by genes in plasmids in host bacteria, and they are finally screened. This is a process of site-specific mutagenesis at the restricted sited of 5 specific residues. LEAD (single mutation) and super-LEAD (multiple mutation) proteins are produced and screened with in the 3.2 x 106 different protein sequences corresponding to all 20 occurring amino acids. Codons of the genes in the plasmids are altered to result in the mutated proteins. The specific number of amino acids investigated was 5.

The Examiner urges that Ladner *et al.* fails to teach increased resistance to proteolysis as a result of mutations, but that such teaching is supplied by Alam *et al.* The Examiner concludes:

> it would have been obvious to someone or ordinary skill in the art at the time of the instant invention to practice Ladner et al. in view of Alam et al. to result in the instantly claimed invention because Alam et al. has the advantage of applying the site directed mutagenesis study of Ladner et al. to the claimed condition of mutation to make resistant to proteolysis.

This rejection respectfully is traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)); and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one of ordinary skill in the art is not

synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v. Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

The claims

The claims are discussed above. Dependent claims include embodiments in which the property to be modified is protease resistance, including increased protease resistance.

Differences between the teachings of the cited references and the claimed methods

Ladner *et al.*

Ladner *et al.* is discussed above. As discussed above, Ladner *et al.* fails to teach or suggest several elements of the claims including a method (claim 1 and dependents) that includes one or more of the steps of:

(1) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein:

each candidate LEAD protein contains a single amino acid replacement, and each replacement is at the same is-HIT locus, wherein each candidate LEAD is the same;

each nucleic acid in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide, whereby the members of each set differ by one amino acid from the members of each of the other sets;

each set is separate from all other sets;

(2) producing a collection of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein:

each encoded candidate LEAD protein contains a single amino acid replacement;

each replacement is at the same is-HIT locus, whereby each candidate LEAD protein is the same;

each nucleic acid molecule in a set encodes the same candidate LEAD protein that differs by one amino acid from the target protein or peptide, whereby the members of each set differ by one amino acid from the members of each of the other sets;

each set is separate from each and all other sets;

(3) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such identified proteins is designated a LEAD mutant protein.

Further Ladner *et al.* fails to disclose a method that includes any or all of the steps of (claim 28 and dependents):

(1) preparing variant nucleic acid molecules encoding variant proteins, wherein each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid at one locus from the target protein at one is-HIT target residue;

(2) separately introducing the nucleic acid molecules encoding each candidate LEAD protein into hosts for expression thereof, and expressing the nucleic acid molecules encoding each variant protein to produce sets of LEAD proteins, wherein:

each candidate LEAD protein in a set contains the same amino acid replacement;

each candidate LEAD protein contains a single amino acid replacement; and

each replacement is at the same locus;

(3) individually screening each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

Alam *et al.*

Alam *et al.* teaches that the region from amino acids 134-150 of hGH is cleaved by plasmin and thrombin and describes a hGH mutant (Arg to Asp at amino acid position 134 and Thr to Pro at amino acid position 135) that is resistant to proteolytic cleavage by thrombin. Alam *et al.* provides no teachings or suggestions regarding rational methods of protein evolution nor one in which amino acids are modified and tested one-by-one. Thus, Alam *et al.* fails to cure the deficiencies in the teachings of Ladner *et al.*

The combination of teachings of Ladner *et al.* and Alam *et al.* does not result in the instantly claimed methods

The combination of teachings of the references fails to teach or suggest a method that includes the above noted steps, including modifying one amino acid at a time and expressing

and screening each modified protein separately to identify LEADs that differ from the original protein at one locus. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 1-3

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* in view of Chiang *et al.* ((1999) *Annual Reviews of Microbiology 53*:129-154) because Ladner *et al.* allegedly teaches all elements of claims 1-3, "except for teach use of solid support with wells to analyze each specie of protein," which teaching allegedly is supplied by Chiang *et al.*, which the Examiner states teaches that "mutagenized bacterial strains are stored individually in arrays." The Examiner concludes that:

> it would have been obvious to someone or ordinary skill in the art at the time of the instant invention to practice Ladner *et al.* in view of Chiang et al to result in the instantly claimed invention because Chiang *et al.* has the advantage of applying the site directed mutagenesis study of Ladner *et al.*. to the claimed condition of wells on a solid support.

This rejection respectfully is traversed.

Analysis

Ladner *et al.*

Ladner *et al.* is discussed above. As discussed above, Ladner *et al.* fails to teach or suggest several elements of the claims, including modifying amino acids in a target region one-by-one, expressing the modified proteins individually and screening them individually. As discussed above, Ladner *et al.* modifies one or more amino acids and produces mixtures of modified proteins that are screened.

Chiang *et al.*

Chiang *et al.*, which is a review article describing various bacterial screening assay systems to identify the function of bacterial genes, is of little relevance to the instant claims. It does not teach any methods for modifying proteins and it fails to cure the deficiencies in the teachings of Ladner *et al.*

The combination of teachings of Ladner *et al.* and Chiang *et al.* does not result in the instantly claimed methods

The combination of teachings of the references fails to teach or suggest a method that includes the above noted steps, including modifying one amino acid at a time and expressing and screening each modified protein separately. Therefore the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 1 and 79

Claims 1 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* in view of Jones *et al.* ((1992) *CABIOS 8*:275-282), because Ladner *et al.* allegedly teaches all elements of claims 1 and 79, except for PAM matrices, which are taught by Jones *et al.* The Examiner concludes:

> it would have been obvious to someone or ordinary skill in the art at the time of the instant invention to practice Ladner *et al.* in view of Jones *et al.* to result in the instantly claimed invention because Jones et al. has the advantage of applying the site directed mutagenesis study of Ladner *et al.* to the claimed analysis condition of PAM matrices.

This rejection respectfully is traversed.

As discussed above, **Ladner *et al.***. fails to teach or suggest several elements of the claims, including modifying amino acids in a target region one-by-one, expressing the modified proteins individually and screening them individually. As discussed above, Ladner *et al.* modifies one or more amino acids and produces mixtures of modified proteins that are screened. These elements are not supplied by **Jones *et al.***, which describes PAM matrices.

Therefore, the combination of teachings of Ladner *et al.* and Jones *et al.*, singly or in any combination thereof, does not result in any of the instantly claimed methods. Thus, the Examiner has failed to set forth a *prima facie* case of obviousness.

THE REJECTION OF CLAIMS 1, 4-11, 15 and 79-81 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 4-11, 15, and 79-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 250, 251, 256-264, and 268-269 of copending U.S. Application Serial No. 10/658,834 because:

> while the claims of the reference are generic to the instant application, the specification of the reference specifically discloses [U.S. Application Serial No. 10/658,834] the species employed in the claims of the instant application.
>
> The two main issues are the facts that in the independent claim (claim 1): (1) each set of nucleic acid molecules in the instant application are individually introduces into host cells and (2) each LEAD protein In a set contains the same amino acid replacement. These species are disclosed in paragraphs [0149] and [0130] of the reference specification which states [0149], "As used herein, a population of sets of nucleic acid molecules encoding a collection (library)of mutants refers to a collection of plasmids or other vehicles that carry (encode) the gene variants, such that individual plasmids or other individual vehicles carry individual gene variants. Each element (member) of the collection is physically separated from the others, such as individually in an appropriate addressable array, and has been

> generated as the single product of an independent mutagenesis reaction." Paragraph [0130] states, "Thus, a plurality of mutant protein molecules are produced, whereby each mutant protein contains a single amino acid replacement at only one of the is-HIT target positions." Thus, while individual replacements are introduced into host cells, each LEAD protein in a set contains the same amino acid replacement.

It respectfully is submitted that cancellation of claims 250, 251, 256-264, and 268-269 in the response, mailed October 20, 2006, in connection with copending U.S. Application Serial No. 10/658,834 has rendered this ground for rejection moot. Nevertheless this rejection respectfully is traversed.

Relevant law

Obviousness-type double patenting occurs when the difference between a first-patented invention and a later claimed invention involves only an unpatentable difference, such that grant of the second patent would extend the right of exclusivity conferred by the first patent. See, e.g., General Foods Corp. v. Studiengesellschaft Kohle mbH, 23 USPQ2d 1839, 1845 (Fed. Cir. 1992). Analysis for obvious-type double patenting involves a comparison of the claims at issue "with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." Id. (emphasis in original); see, also, Ortho Pharm. Corp. v. Smith, 22 USPQ2d 1119, 1125 (Fed. Cir. 1992) ("It is the claims, not the specification that defines an invention [citation] . . . [a]nd it is the claims that are compared when assessing double patenting."). ***Thus, an obviousness-type double patenting rejection is based on the claims and not on the disclosure of a patent.***

The comparison between claims in an obviousness-type double patenting inquiry requires the use of a fundamental rule of claim construction, that the invention is defined by the claim taken as a whole – every claim limitation (or each step) being material to the description of the invention. Ortho Pharm. Corp., 22 USPQ2d at 1125. Thus, it is inappropriate to base an obviousness-type double patenting rejection on the disclosure of a patent, even when such disclosure is found in the claims. Only the claims are considered in determining whether obviousness-type double patenting exists and they are not used as disclosure but are interpreted based on the rules of claim construction.

Obviousness-type double-patenting has not been found when claims at issue do not embrace the prior patent compounds and/or the claims in the prior patent do not suggest any

modification that would have produced the claimed compounds in the patent or application at issue. See, e.g., Id. In Ortho, obvious-type double patenting was not found in an instance in which the claims in the patent at suit were directed to compounds that did not encompass, structurally, the compounds claimed in the prior patents, and the claims in the prior patents did not suggest a modification (based upon the principles of claims interpretation) of their compounds to produce compounds claimed in the patent at suit.

Analysis

The Examiner states that the claims of copending U.S. Application Serial No. 10/658,834 are generic to the instant claims, and then relies upon the disclosure of the copending application to assess obviousness-type double patenting. This analysis is incorrect on two grounds. First, in setting forth the rejection, the Examiner has improperly relied upon the specification of the copending application. This is **not permitted** in considering the issued obviousness-type double patenting. As discussed above, obviousness-type double patenting is a judicially created doctrine designed to prevent improper extension of a right of exclusivity granted by the claims of a patent. In assessing the right of exclusivity, the claims of the prior patent are assessed based upon the rules of claim construction. The claims nor the rest of the specification cannot be employed as disclosure. Hence, it respectfully is submitted that the premise upon which the rejection is made is incorrect.

Second, the claims in the copending application are not necessarily generic to the instant claims. Claim 250 and dependent claims are directed to a method in which the target protein is modified to achieve increased resistance to proteases. The instant independent claims do not specify the property that is modified, and hence are more generic. Claim 256 is directed to the 3-D method disclosed in the application, and, thus, is not generic to any of the instant claims.

Notwithstanding this, as noted above, cancellation of claims 250, 251, 256-264, and 268-269 in the response, mailed October 20, 2006, in connection with copending U.S. Application Serial No. 10/658,834 has rendered this ground for rejection moot.

THE REJECTION OF CLAIMS 1, 4-11, 15 AND 79-81 UNDER 35 U.S.C. §102(f)

Claims 1, 4-11, 15 and 79-81 are rejected under 35 U.S.C. §102(f) because co-pending application U.S. Application Serial No. 10/658,834 allegedly contains claims that are not patentably distinct from the instant application. This rejection respectfully is traversed.

As discussed above with respect to the rejection for obviousness-type double patenting, the instant claims are patentably distinct. Notwithstanding this, it respectfully is submitted that the rejection is without merit. The applications indeed have different inventive entities; the inventors of the claims in the copending application are subset of the inventors named in this application. The inventors named in the copending application are: Manuel Vega, Lila Drittanti, Rene Gantier and Thierry Guyon. The inventors named in the instant application include these four individuals plus Hugo Cruz Ramos. Inventorship of the application includes the inventors who contributed to any claim; each claim can have a different inventive entity. In this instance, claims have different inventive entities. There is no logical inconsistency upon which to base this rejection, since the claims in copending application are directed to a different method from that claimed in this application and also include claims to many mutant cytokine polypeptides. To set forth a rejection under 35 U.S.C. §102(f), there must be more than a difference in the inventive entity; there must be something more from which an error in naming inventors can be inferred. See *In re Katz*, 215 USPQ 14 (CCPQ 1982). Hence, there is no basis upon which to make this rejection.

Since the Office has raised the issue, however, inventorship has been reviewed with the owner and with inventors of the application to confirm that each has made inventive contributions to one or more of the original claims. A DECLARATION under 37 C.F.R. §1.132 of Dr. Manuel Vega is attached hereto. As indicated in the DECLARATION, each named inventor made an inventive contribution to one or more of the original claims in the application. In addition, Hugo Ramos Cruz was named as an inventor on this application because of his contributions to the aspect of the method directed to embodiments, such as claim 18, in which "each is-HIT target amino acid is susceptible to digestion by one or more proteases." Hugo Ramos Cruz is not a joint inventor of any of claims 1, 4-11, 15 and 79-81.

* * *

In view of the above, reexamination and allowance of the application are respectfully requested.

Respectfully submitted,

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